JEM Journal of Experimental Medicine 125 years

VIEWPOINT

JEM 125th Anniversary

The life of B cells according to *JEM*

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Our understanding of the generation and function of B lymphocytes is well represented by publications in *JEM*, including numerous landmark studies on normal B cell immunology. This viewpoint reflects on a selection of such high-impact studies.

B lymphocytes are essential components of the adaptive immune system and have a major role in immune reactions as producers of antibodies to combat infectious agents. During B cell development in the bone marrow, each B cell is equipped with a unique B cell antigen receptor (BCR), the membrane anchored form of antibodies. This happens through a sophisticated multistep process of V(D)J recombination that assembles the variable (V) regions of the antibody (Ig) heavy and light chain genes. For the analysis of the early stages of B cell development in the mouse, a delineation of pro- and pre-B cells into three subpopulations (fractions A, B, and C) and their initial phenotypic, genetic, and functional characterization was highly influential (Hardy et al., 1991). A major intrinsic problem of the random assembling of the antibody binding sites of the BCR during B cell development is that also many autoreactive specificities will be generated that hence pose a risk for the development of autoimmune diseases. Besides deletion of autoreactive immature B cells, a more economic strategy to escape autoreactivity was revealed by Tiegs et al. (1993) and Gay et al. (1993) by showing that autoreactive immature B cells in the bone marrow can replace their rearranged Ig light chain genes through novel light chain rearrangements, termed receptor editing (see figure). There is a good chance that this editing eliminates autoreactivity of the BCR. The final stages of B cell development into the mature B cell pool take place in the murine spleen. This occurs at two distinct steps that were defined and characterized as transitional B cells type 1 and 2, and that is guided by BCR signaling (Loder et al., 1999).

Once B cells enter the pool of naive, mature B cells, they recirculate through the body. Naive B cells have a restricted life span, and it was therefore important to reveal which factors are involved in regulating their survival. In this regard, the identification of a key role of B cell activating factor (BAFF), which binds to the B cell maturation antigen (BCMA) on naive B cells, in supporting the survival of naive B cells was a landmark finding for our understanding how the homeostasis of the naive B cell pool is regulated (Thompson et al., 2000).

Already ∼50 yr ago, studies in the mouse indicated that the pool of mature naive B cells is not homogeneous, but that distinct sublineages of B cells exist. A main distinction was made into mostly CD5$^+$ B1 B cells and follicular and marginal zone B2 cells. Murine B1 cells play a major role in producing natural IgM and are predominantly involved in T cell–independent immune responses. A first definition and detailed characterization of the CD5$^+$ B cell subset in mice was provided by Hayakawa et al., (1983). It was a decade-long discussion of how the B cell sublineages are established, with major contributions published in *JEM*. The first landmark study for this debate indicated that B1 and B2 cells derive from distinct progenitors, with bone marrow progenitors for B1 cells predominantly restricted to young mice (Hayakawa et al., 1985).

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The germinal center (GC) is the histological structure in secondary lymphoid organs (e.g., lymph nodes and the spleen) in which the main steps of T cell–dependent (TD) immune reactions take place, and where memory B cells and long-lived plasma cells are generated (see figure). In the GC, antigen-activated B cells undergo massive clonal expansion and activate the process of somatic hypermutation (SHM) to generate BCR variants. B cells expressing BCR with increased affinity are selected by GC T helper cells, a process termed affinity

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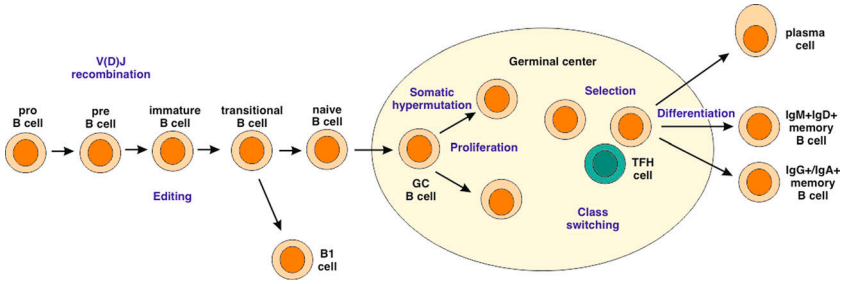

Outline of B cell development and differentiation.

maturation. GC B cells undergo multiple rounds of proliferation, mutation, and selection, but eventually, positively selected GC B cells differentiate into memory B cells or plasma cells and exit the GC microenvironment. Many GC B cells also undergo class-switch recombination of the Ig heavy chain, so that the GC is the main structure where IgG-, IgA-, and IgE-expressing B cells are generated. Soon after the receptor CD40 and its ligand CD40L were identified as central costimulatory factors for B cell–T cell interaction, it was revealed that this interaction is indeed essential for the GC reaction and memory B cell generation (Foy et al., 1994). 16 yr later, two studies published in *JEM* uncovered a further central costimulatory factor of GC T helper cells for GC B cells, namely IL21 (Zotos et al., 2010; Linterman et al., 2010). IL21 is important for the maintenance of the GC response, and this is partly mediated by promoting expression of BCL6, the master transcription factor for the GC B cell gene expression program, in GC B cells.

Rearranged IgV genes represent ideal clonal markers for B cells, and the presence and pattern of somatic mutations in these genes is very informative regarding the differentiation stage and B cell intraclonal diversification patterns. Therefore, sequencing studies of IgV genes obtained from microdissected B cell pools at defined locations in lymphoid organs and specific stages of an immune response were very informative to clarify the architecture and dynamics of TD immune responses. In this regard, a collection of articles by G. Kelsoe and his co-workers in *JEM* were highly influential. For example, in one of these studies it was shown that in TD immune responses there is first a wave of oligoclonal B cell proliferation without SHM in primary foci in the T cell zone, and that some of the primary focus B cells then seed GC in B cell follicles where SHM is initiated (Jacob and Kelsoe, 1992).

As positively selected GC B cells have two very different differentiation potentials—memory B cells or plasma cells—it is obviously critical to understand how the decision to develop along the one or the other pathway are regulated. Several landmark studies indicated that BCR affinity plays a decisive role in this regard, including a study by Phan et al. (2006), which showed that high-affinity GC B cells preferentially become plasma cells. Many plasma cells then home to the bone marrow, where they can survive for a long time. For this long-term survival, expression of BCMA on plasma cells is essential (O'Connor et al., 2004). The ligands for BCMA signaling, APRIL (a proliferation-inducing ligand) and BAFF, are provided by other cells in the plasma cell niche.

When more and more B cell differentiation markers became available for flow cytometric analysis, and the sequence analysis of IgV genes became easier through the development of polymerase chain reaction-based molecular studies in the early nineties of the last century, a wealth of influential studies appeared that aimed at mapping and characterizing in particular the human B cell system. *JEM* became the home for several high-impact studies in this field. The first study to be mentioned in this regard defined and ordered five mature human tonsillar B cell subsets (Pascual et al., 1994). The markers IgD and CD38 became widely used to distinguish tonsillar naive (IgD^+CD38^-) from class-switched memory (IgD^-CD38^-) and GC B cells (IgD^-CD38^+), although it is now clear that these definitions are too simplistic. A few years later, a study from our own group proposed CD27 as a general marker for human memory B cells, and that also a substantial fraction of IgM^+IgD^+ B cells are post-GC memory B cells, namely those expressing CD27 (Klein et al., 1998). This was based on the detection of somatically mutated IgV genes in all subsets of $CD27^+$ B cells. CD27 expression on non-GC B cells (human GC B cells and plasma cells are also $CD27^+$) became a widely accepted marker for human memory B cells. It later became clear that also $CD27^-IgG^+$ and some $CD27^-IgM^+$ human B cells with mutated IgV genes exist, likely representing $CD27^-$ memory B cells. A study by Tangye et al. (1998) demonstrated that the human splenic marginal zone is dominated by $CD27^+$ B cells with mutated IgV genes that hence were also regarded as memory B cells (note that in the mouse, splenic marginal zone B cells are mostly unmutated and pre-GC B cells). However, a debate about the origin and identity of mutated IgD^+IgM^+ human B cells developed, again with major contributions in this journal. In particular, it was proposed that the mutated IgM^+IgD^+ B cells derive from T cell–independent immune responses and hence independent from a GC reaction (Kruetzmann et al., 2003), or through a primary antigen-independent diversification pathway, at least in young children (Weller et al., 2008). Further support for a mostly GC-derived origin and hence TD memory identity of $IgD^+IgM^+CD27^+$ B cells in human adults was provided by demonstrating that these cells often derive from common clones with classical IgG^+ memory B cells, and that they frequently carry *BCL6* gene mutations as a genetic trait of a GC passage (Seifert and Küppers, 2009).

In conclusion, numerous landmark studies for our understanding of the generation and functions of B cells were published in *JEM*, which this year celebrates its 125th birthday, so that a comprehensive picture of B cell immunology emerges from these analyses (see figure). The journal has also been and is a valuable platform for controversial discussions, debated at high scientific level. As this viewpoint is restricted to normal B cell development and differentiation, it should be pointed out that *JEM* also has a remarkable history of publishing highest impact studies on B cells in immunodeficiency and autoimmune diseases and the pathogenesis of B cell malignancies.

Acknowledgments

I especially thank Klaus Rajewsky as my prior teacher and mentor for introducing

me to B cell immunology and for teaching me scientific thinking. I am also thankful to all prior and present group members, as well as my long-term collaborator Martin-Leo Hansmann. I apologize that due to format restrictions, often only one of several similar and concurrent high-quality studies could be cited, and that because of the focus on landmark articles in *JEM*, related studies in other journals are not considered here.

Present work of our group on B cells is supported by the Deutsche Forschungsgemeinschaft (KU1315/10-1, KU1315/14-1), the Wilhelm Sander Stiftung (2018.101.1), and the Deutsche José Carreras Leukämie Stiftung (DJCLS 02 R/2020).

Disclosures: The author declares no competing financial conflicts.

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